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In This Issue

Statin Dose and Degree of LDL Reduction

The National Cholesterol Education Program (NCEP) recently updated the recommendations for prevention and treatment of coronary heart disease (CHD).[1] Lifestyle modification is suggested as an initial preventive measure, followed by pharmacological intervention when other efforts are deemed ineffective. The NCEP guidelines recommend specific low-density lipoprotein (LDL) cholesterol ranges based on cardiovascular risk categories. In patients with documented CHD or who have CHD risk equivalents, a target LDL of less than 100 mg/dL is recommended. A target LDL of less than 130 mg/dL is recommended for patients who have two or more risk factors (e.g., cigarette smoking, blood pressure ≥ 130 mmHg, high density lipoprotein (HDL) < 40 mg/dL, family history of premature CHD, males > 45 years of age, females > 55 years of age). In those who have only one or no risk factors, a target LDL of less than 160 mg/dL is recommended. The American Diabetes Association recommends an LDL target of less than 100 mg/dL in patients with diabetes.[2]

The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors ("statins") have emerged as essential agents for achieving LDL goals in patients with persistent hyperlipidemia, despite lifestyle modification. The potent LDL-lowering activity and proven reduction in cardiovascular mortality associated with these agents has solidified the role of the statins in the management of CHD. All statins lower LDL and total cholesterol; however, the degree to which the available agents lower cholesterol concentrations is variable. This variability should be considered when changes are made from one statin to another because of financial considerations or formulary restrictions. Because direct comparison of the LDL lowering ability of the currently marketed statins has been limited, equivalent dosages were often based on indirect comparison of the LDL lowering ability of these agents. These data, however, may not be appropriate for determining equivalent dosages of statins because of inherent differences in study patients and study designs. Prospective data based on direct comparisons of the LDL-lowering effects of the statins is a more ideal method for estimating dosage equivalence.

The CURVES study directly compared the hypolipidemic effect of atorvastatin to that of simvastatin, pravastatin, lovastatin, and fluvastatin at various doses.[3] Patients with elevated LDL cholesterol (≥160 mg/dL) at two consecutive measurements were initiated on the American Heart Association (AHA) Step I diet for 6 weeks. If LDL cholesterol remained elevated, patients were randomized to one of 15 statin regimens. Data from this study suggest that atorvastatin 10 mg daily was similar in LDL lowering to lovastatin 80 mg daily, pravastatin 40 mg daily, and simvastatin 20 mg or 40 mg daily. Other dosing regimens were not as effective as atorvastatin 10 mg daily. Atorvastatin 20 mg daily was similar in LDL lowering ability to lovastatin 80 mg daily and superior to all other dosing regimens. It should be noted that this investigation did not report the effects of simvastatin 80 mg daily on LDL cholesterol. The effects of statins on LDL cholesterol at various doses in this study are summarized in Table 1.

Cerivastatin 0.4 mg and 0.8 mg given once daily was also compared to atorvastatin 10 mg and 20 mg daily, respectively.[4] Patients who were already receiving lipid-lowering agents were asked to discontinue these medications and adhere to the AHA Step I diet for 10 weeks. Patients with elevated lipid measurements after this 10-week run in period

Table 1

Mean reduction in LDL cholesterol reported in the CURVES[3] and CAVEAT[4] trials compared to mean reduction in LDL cholesterol reported in the statin prescribing information.[5-10]

Statin	Daily Dose	Mean Reduction in LDL Cholesterol Reported in CURVES and CAVEAT	Mean Reduction in LDL Cholesterol Reported in Prescribing Information
Atorvastatin	10mg	-38%[3] / -37%[4]	-39%[5]
	20mg	-46%[3] / -42%[4]	-43%[5]
	40mg	-51%[3]	-50%[5]
	80mg	-54%[3]	-60%[5]
Cerivastatin	0.2mg	NR	-25%[6]
	0.3mg	NR	-31%[6]
	0.4mg	-34%[4]	-34%[6]
	0.8mg	-43%[4]	-42%[6]
Fluvastatin	20mg	-17%[3]	-22%[7]
	40mg	-23%[3]	-25%[7]
	80mg	NR	-35%[7]
Lovastatin	10mg	-29%[3]	-21%[8]
	20mg	-31%[3]	-24% to -27%[8]
	40mg	-48%[3]	-30% to -32%[8]
	80mg	NR	-40% to -42%[8]
Pravastatin	10mg	-19%[3]	-22%[9]
	20mg	-24%[3]	-32%[9]
	40mg	-34%[3]	-34%[9]
Simvastatin	5mg	NR	-26%[10]
	10mg	-28%[3]	-30%[10]
	20mg	-35%[3]	-38%[10]
	40mg	-41%[3]	-29% to -41%[10]
	80mg	NR	-36% to -47%[10]

NR = Not reported

were randomized to one of four lipid lowering regimens (See Table 1). Atorvastatin 10 mg daily produced a significantly greater reduction in LDL cholesterol compared to cerivastatin 0.4 mg daily (-37.2% vs. -34.1%, respectively; $p<0.05$). No difference was detected between atorvastatin 20 mg and cerivastatin 0.8 mg daily (-41.7% vs -42.7%, respectively).

References available upon request

Mesalamine (Asacol®): A Brief Review

Introduction

Ulcerative colitis (UC) affects approximately 250,000 Americans, with an incidence of 2-6 per 100,000 people per year.[1] UC is an inflammatory bowel disease characterized by diffuse mucosal inflammation that is generally limited to the colon. The classic presenting symptom of UC is bloody diarrhea, which may be accompanied by cramping and weight loss. Patients experience acute exacerbations followed by remissions. The goal of disease management is to minimize symptoms and prolong remissions to improve patients' quality of life. Aminosalicylates were the first category of drugs shown to be beneficial in UC.[2] The 5-aminosalicylate, also known as mesalamine, was identified as the active component in the late 1970s. Mesalamine is indicated for use in mild to moderately active ulcerative colitis and for maintaining remission. Other therapies utilized in the management of ulcerative colitis include corticosteroids (topical and systemic), immunosuppressants (azathioprine, mercaptopurine, and methotrexate), and infliximab.

Description

Asacol® is manufactured by Procter & Gamble in the form of a delayed-release tablet containing 400 mg of mesalamine. Mesalamine is also commercially available as a controlled-release capsule (Pentasa®, Shire US) and rectal suspension enema or suppository (Rowasa®, Solvay Pharmaceuticals).

Indications

Mesalamine is FDA-approved for the treatment of mildly to moderately active ulcerative colitis and for the maintenance of remission.

Pharmacology

Mesalamine (5-aminosalicylic acid) is the active component of the anti-inflammatory agent sulfasalazine. The sulfa moiety is cleaved by bacterial action in the colon to produce mesalamine. The exact mechanism of action is unknown. Mesalamine may act topically to

block cyclooxygenase and inhibit prostaglandin (PG) production in the colon.[3] Mucosal production of arachidonic acid (AA) metabolites, both through the cyclooxygenase and lipoxygenase pathways, is increased in patients with chronic inflammatory bowel disease.

Pharmacokinetics

Asacol® tablets are coated with a pH-sensitive acrylic-based resin that delays release of mesalamine until it reaches the distal ileum and colon. Only 28% is absorbed following oral administration. Neither the extent nor rate of absorption is affected by the presence of food. The absorbed mesalamine is rapidly acetylated in the gut mucosal wall and by the liver. Approximately 21% of an oral dose is excreted by the kidney as N-acetyl-5-aminosalicylic acid. The remaining drug that is not absorbed is available for topical action and is eliminated in the feces. The t_{max} for mesalamine and its metabolite, N-acetyl-5-aminosalicylic acid, is usually delayed, reflecting the delayed release, and ranges from 4 to 12 hours. The half-lives of elimination for mesalamine and N-acetyl-5-aminosalicylic acid are usually about 12 hours.[3]

Selected Clinical Studies

Mildly to moderately active ulcerative colitis

Oral delayed-release mesalamine has been shown to be effective in patients with mild to moderately active ulcerative colitis at doses $\geq$ 2.4 mg/day in a number of clinical trials. One multi-center, randomized, double-blind study of 158 patients compared the use of delayed-release mesalamine 1.6 g/day and 2.4 g/day to placebo for 6 weeks. At the dose of 2.4 g/day, 21 of 43 (49%) mesalamine patients showed sigmoidoscopic improvement of the bowel compared to 12 of 44 (27%) placebo patients ($p = 0.048$). In addition, symptoms improved in significantly more patients in the mesalamine 2.4 g/day group experiencing decreased rectal bleeding and stool frequency.[4] A dose-response relationship was illustrated in a 1990 study in which patients with active disease receiving mesalamine 3.6 g/day achieved superior endoscopic response and remission rates compared to the 1.2 g/day group.[5]

Maintenance of remission of ulcerative colitis

Oral delayed-release mesalamine has effectively maintained remission for patients with ulcerative colitis in studies ranging from 4-12 months. Remission is defined as the period of time between relapses. The definition of relapse varies between trials, ranging from endoscopic findings independent of symptoms to severe symptoms independent of endoscopic findings.[6] One multi-center, randomized, double-blind study of 264 patients compared the use of delayed-release mesalamine 0.8 g/day (n = 90) or 1.6 g/day (n = 87) to placebo (n = 87) for 6 months. In an intention-to-treat analysis of the 174 patients treated with mesalamine 1.6 g/day or placebo, the mesalamine group maintained endoscopic remission of ulcerative colitis in 61 of 87 (70.1%) of patients, compared to 42 of 87 (48.3%) of placebo recipients ($p = 0.005$). The difference in endoscopically-proven remission maintenance between patients treated with mesalamine 0.8 g/day (40/68 patients; 58.8%) and placebo (25/63 patients; 39.7%) was not statistically significant ($P=0.05$).[7] In comparison with sulfasalazine 2-4 g/day, delayed-release mesalamine 0.8-1.6 g/day produced equivalent remission rates of 61 vs 62%, respectively.[8]

Combination therapy and other uses

While oral mesalamine has been shown to be effective as monotherapy, the addition of a rectal mesalamine enema can provide additive symptomatic improvement. A study evaluating oral delayed-release mesalamine 2.4 g/day and mesalamine 4g suspension enema once nightly, as monotherapy and in conjunction, found the combination to produce significantly better symptomatic results according to the physicians' global assessment (45 vs 85%, $p<0.05$).[9]

There are fewer clinical trials regarding the efficacy of mesalamine in Crohn's disease, yet its use is considered part of the standard of care. However, the Pentasa® extended-release preparation is considered the preferred oral delivery system due to the more diffuse involvement of the intestines in Crohn's disease compared to ulcerative colitis.[10]

Adverse Effects

Oral delayed-release mesalamine is generally well-tolerated. Nausea, diarrhea and dyspepsia occur in 2-4% patients receiving mesalamine compared to 0-2% in patients receiving placebo.[4] The incidence of side effects does not appear to be dose-dependent. Rarely, exacerbations of the symptoms of colitis, characterized by cramping, abdominal pain, bloody diarrhea, and occasionally by fever, headache, malaise, pruritus, rash, and conjunctivitis, have been reported after the initiation of mesalamine. Symptoms usually abate when therapy is discontinued. Renal impairment, including minimal change nephropathy, and acute and chronic interstitial nephritis, has been reported.

Drug Interactions

Although not well documented, the concomitant use of lactulose may acidify the colonic lumen and lower stool pH, which would affect the pH-dependent delayed drug release.[6]

Precautions and Contraindications

Mesalamine is contraindicated in patients with hypersensitivity to salicylates. Patients with pyloric stenosis may have prolonged gastric retention of Asacol® tablets, which could delay release of mesalamine in the colon. Renal impairment, including minimal change nephropathy, and acute and chronic interstitial nephritis, has been reported in patients taking Asacol® tablets as well as other compounds which contain or are converted to mesalamine. Therefore, caution should be exercised when using mesalamine in the elderly and in patients with known renal dysfunction or history of renal disease. Some suggest that serum creatinine levels be monitored every four

weeks for the first 3 months, every 3 months for one year and annually thereafter.[11] Use of mesalamine is contraindicated in children less than 2 years old. A 1995 abstract presented retrospective data suggesting that use of mesalamine for Crohn's disease or ulcerative colitis in patients aged 4 to 19 years was well tolerated.[12] Mesalamine is designated as FDA Pregnancy Category B.

Dosage and Administration

Treatment of mildly to moderately active UC

The usual dosage in adults is two 400-mg tablets taken three times a day for a total daily dose of 2.4 grams for a duration of 6 weeks.

Maintenance of remission of UC

The recommended dosage in adults is 1.6 grams daily, in divided doses. Treatment duration in prospective, well-controlled trials ranged from 4 to 12 months.

Cost

See table below for cost comparisons.

Drug	Dose	NIH cost per month ($)[a]	AWP per month ($)[b]
Asacol®; treatment of active disease	2.4 g/day	72.86	146.09
Asacol®; maintenance	1.6 g/day	48.58	97.39
Pentasa®	4 g/day	116.08	238.62
Rowasa® enema	60 mL/day	182.96	406.46
Rowasa® suppository	500 mg BID/day	109.55	234.35
Azulfidine-EN® (Sulfasalazine); treatment of active disease	4 g/day	44.02	82.18
Azulfidine-EN® (Sulfasalazine); maintenance	2 g/day	22.01	41.09

[a] Federal Supply Schedule
[b] Average Wholesale Price

Editor's Note

We thank James S. Kalus, Pharm.D. and Nayahmka McGriff, Pharm.D. for their contributions to this issue of *Pharmacy Update*.

Patient Counseling

- Patients should be instructed to swallow the Asacol® tablets whole, taking care not to break the outer coating. The outer coating is designed to remain intact to protect the active ingredient and thus ensure mesalamine availability for action in the colon.
- In 2% to 3% of patients in clinical studies, intact or partially intact tablets have been reported in the stool. If this occurs repeatedly, patients should be instructed to contact their physician.
- Patients with ulcerative colitis should be made aware that ulcerative colitis rarely remits completely, and that the risk of relapse can be substantially reduced by continued administration of mesalamine at a maintenance dosage.

Conclusion

Oral delayed-release mesalamine is a cornerstone of therapy for ulcerative colitis. Asacol® is generally effective and appears to be well tolerated.

References available upon request

FDA Safety Reports

- You can access the latest safety information from the Food and Drug Administration website. To access "Dear Health Professional" letters, other safety notifications, and labeling changes related to drug safety, just point your browser to *www.fda.gov* and click on "MedWatch." MedWatch is the FDA's medical products reporting program.
- You can receive immediate e-mail notification of new material as soon as it is posted on the MedWatch website. Just send a subscription message to *fdalists@archie.fda.gov.* In the message body enter: *subscribe medwatch* and your e-mail address.

Formulary Update

The Pharmacy and Therapeutics Committee recently approved the following formulary changes:

Additions

- Mesalamine (Asacol®), an oral agent (5-aminosalicylic acid) for the treatment of ulcerative colitis
- Pantoprazole (Protonix®), an injectable proton-pump inhibitor approved for the treatment of gastroesophageal refulx disease. At the CC, this agent will be used mostly as an alternative to high-dose ranitidine for acid control in patients with Zollinger-Ellison Syndrome.
- Eptifibatide (Integrilin®), an injectable peptide glycoprotein IIb/IIIa receptor antagonist for the treatment of acute coronary syndrome and in patients undergoing percutaneous coronary intervention
- Metaraminol (Aramine®), an injectable vasopressor that is useful for managing acute hypotension in the setting of a cardiac catheterization laboratory

Deletions

- Abciximab (ReoPro®), an injectable peptide glycoprotein IIb/IIIa receptor antagonist